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I, ADRIAN PAUL BROWN, M.A., M.C.I.L., M.I.T.I., declare

1. That I am a citizen of the United Kingdom of Great Britain and Northern Ireland, residing at 5 Gilbert Road, London, SE11 4NZ.
2. That I am well acquainted with the French and English languages.
3. That the attached is a true translation into the English language of the certified copy of European Patent Application No. 03293085.1 filed on 10th December 2003.
4. That all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such wilful false statements may jeopardise the validity of the patent application in the United States of America or any patent issuing thereon.

DECLARED THIS 5th DAY OF APRIL 2006



A P BROWN

10/582419

1AP20 REC'D PCT/PTO 09 JUN 2006

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European patent application
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européen spécifiée à la
page suivante.

Patentanmeldung Nr. Patent application No. Demande de brevet n°

03293085.1

Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

R C van Dijk

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Application no.: 03293085.1
Demande no:

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Anmelder/Applicant(s)/Demandeur(s):

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Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se référer à la description.)

Nouveau procédé de synthèse de dérivés de l'acide (2S, 3aS, 7aS) - 1 - [(S)-
alanyl]-octahydro-1H-indole-2-carboxylique et application à la synthèse du
perindorpil

In Anspruch genommene Priorität(en) / Priority(ies) claimed /Priorité(s)
revendiquée(s)
Staat/Tag/Aktenzeichen/State/Date/File no./Pays/Date/Numéro de dépôt:

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AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL
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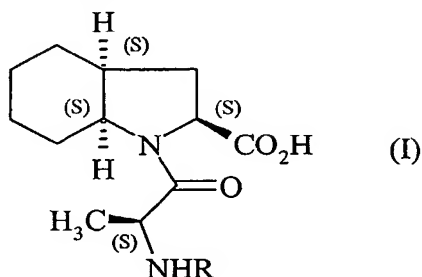
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**NOUVEAU PROCEDE DE SYNTHESE DE DERIVES DE L'ACIDE (2S, 3aS, 7aS)-
1-[(S)-ALANYL]-OCTAHYDRO-1H-INDOLE-2-CARBOXYLIQUE ET
APPLICATION A LA SYNTHESE DU PERINDOPRIL**

**LES LABORATOIRES SERVIER
12, PLACE DE LA DEFENSE
F-92415 COURBEVOIE CEDEX**

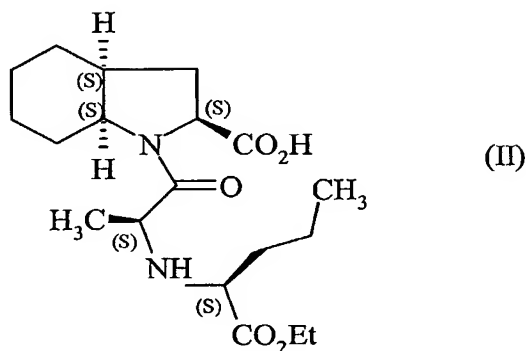
**INVENTEURS : T. DUBUFFET
J-P LECOUBE**

La présente invention concerne un procédé de synthèse des composés de formule (I) :



dans laquelle R représente un atome d'hydrogène ou un groupement protecteur de la fonction amino,

5 et leur application à la synthèse du perindopril de formule (II) :



et de ses sels pharmaceutiquement acceptables.

Le perindopril, ainsi que ses sels pharmaceutiquement acceptables, et plus particulièrement son sel de tert-butylamine, possèdent des propriétés pharmacologiques intéressantes.

10 Leur principale propriété est d'inhiber l'enzyme de conversion de l'angiotensine I (ou kininase II), ce qui permet d'une part d'empêcher la transformation du décapeptide angiotensine I en octapeptide angiotensine II (vasoconstricteur), et d'autre part de prévenir la dégradation de la bradykinine (vasodilatateur) en peptide inactif.

15 Ces deux actions contribuent aux effets bénéfiques du perindopril dans les maladies cardiovasculaires, tout particulièrement l'hypertension artérielle et l'insuffisance cardiaque.

Le perindopril, sa préparation et son utilisation en thérapeutique ont été décrits dans le brevet européen EP 0 049 658.

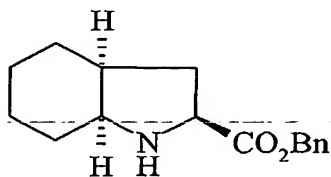
Compte-tenu de l'intérêt pharmaceutique de ce composé, il était important de pouvoir y accéder avec un procédé de synthèse performant, facilement transposable à l'échelle industrielle, conduisant au perindopril avec un bon rendement et une excellente pureté.

Le brevet EP 0 308 341 décrit la synthèse industrielle du perindopril par couplage de l'ester benzylique de l'acide (2*S*, 3*aS*, 7*aS*)-octahydroindole 2-carboxylique avec l'ester éthylique de la N-[(*S*)-1-carboxybutyl]-(*S*)-alanine en présence de dicyclohexylcarbodiimide, suivie de la déprotection du groupement carboxylique de l'hétérocycle par hydrogénation catalytique.

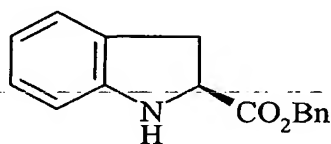
Ce procédé présente des inconvénients liés à l'utilisation du dicyclohexylcarbodiimide.

La Demanderesse a mis au point un procédé de synthèse du perindopril qui utilise d'autres agents de couplage.

Plus spécifiquement, la présente invention concerne un procédé de synthèse du perindopril caractérisé en ce que l'on met en réaction l'ester benzylique de formule (IIIa) ou (IIIb) :



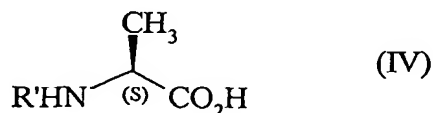
(IIIa)



(IIIb)

ou le sel d'addition de l'ester de formule (IIIa) ou (IIIb) avec un acide minéral ou organique,

avec le dérivé de l'alanine de formule (IV) :



(IV)

dans laquelle R' représente un groupement protecteur de la fonction amino,

en présence d'un agent de couplage choisi parmi les réactifs et couples de réactifs suivants :

(1,3-diméthylaminopropyl)-3-éthyl-carbodiimide chlorhydrate,

(1,3-diméthylaminopropyl)-3-éthyl-carbodiimide chlorhydrate / 1-hydroxybenzotriazole,

5 (1,3-diméthylaminopropyl)-3-éthyl-carbodiimide chlorhydrate/1-hydroxy-7-azabenzotriazole,

(1,3-diméthylaminopropyl)-3-éthyl-carbodiimide chlorhydrate / N-hydroxysuccinimide,

(1,3-diméthylaminopropyl)-3-éthyl-carbodiimide chlorhydrate / 3-hydroxy-3,4-dihydro-4-oxo-1,2,3-benzotriazine,

10 (1,3-diméthylaminopropyl)-3-éthyl-carbodiimide chlorhydrate / N-hydroxyphthalimide,
dicyclohexylcarbodiimide / 1-hydroxy-7-azabenzotriazole,
dicyclohexylcarbodiimide / N-hydroxysuccinimide,
dicyclohexylcarbodiimide / 3-hydroxy-3,4-dihydro-4-oxo-1,2,3-benzotriazine,
dicyclohexylcarbodiimide / N-hydroxyphthalimide,

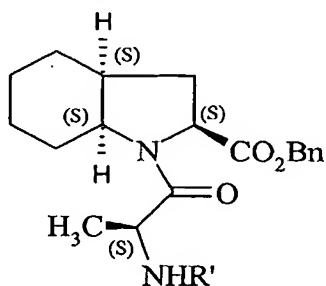
15 O-(benzotriazol-1-yl)-1,1,3,3-tétraméthyluronium hexafluorophosphate,
O-(7-azabenzotriazol-1-yl)-1,1,3,3-tétraméthyluronium hexafluorophosphate,
O-(benzotriazol-1-yl)-1,1,3,3-tétraméthyluronium tétrafluoroborate,
benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate,
benzotriazol-1-yl-oxy-tris-(diméthylamino)-phosphonium hexafluorophosphate,

20 O-(benzotriazol-1-yl)-1,1,3,3-bis(tétraméthylène)-uronium hexafluorophosphate,
O-(benzotriazol-1-yl)-1,1,3,3-bis(pentaméthylène)-uronium hexafluorophosphate,
chloro-tripyrrolidinophosphonium hexafluorophosphate,
chloro-1,1,3,3-bis(tétraméthylène)-formamidinium hexafluorophosphate,
chloro-1,1,3,3-bis(pentaméthylène)-formamidinium hexafluorophosphate,

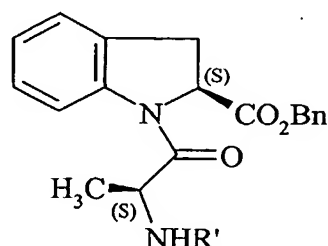
25 N-éthoxycarbonyl-2-éthoxy-1,2-dihydroquinoléine,
O-[(éthoxycarbonyl)-cyanométhylénamino]-1,1,3,3-tétraméthyluronium tétrafluoroborate,
O-(3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl)-1,1,3,3-tétraméthyluronium
tétrafluoroborate,

O-(3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl)-1,1,3,3-tétraméthyluronium
30 tétrafluoroborate / 1-hydroxybenzotriazole,

- O-(3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl)-1,1,3,3-tétraméthyluronium tétrafluoroborate /N-méthylmorpholine,
O-(3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl)-1,1,3,3-tétraméthyluronium tétrafluoroborate /collidine,
5 O-(1,2-dihydro-2-oxo-1-pyridyl)-1,1,3,3-tétraméthyluronium tétrafluoroborate,
O-(1,2-dihydro-2-oxo-1-pyridyl)-1,1,3,3-tétraméthyluronium tétrafluoroborate/1-hydroxy-benzotriazole,
O-(1,2-dihydro-2-oxo-1-pyridyl)-1,1,3,3-bis(tétraméthylène)-uronium hexafluorophosphate,
10 O-(1,2-dihydro-2-oxo-1-pyridyl)-1,1,3,3-bis(tétraméthylène)-uronium hexafluorophosphate/1-hydroxy-benzotriazole,
O-(N-succinimidyl)-1,1,3,3-tétraméthyluronium tétrafluoroborate,
O-(N-succinimidyl)-1,1,3,3-bis(tétraméthylène)uronium tétrafluoroborate,
O-(N-succinimidyl)-1,1,3,3-bis(tétraméthylène)uronium tétrafluoroborate/1-hydroxy-
15 benzotriazole,
O-(5-norbornène-2,3-dicarboximido)-1,1,3,3-tétraméthyluronium tétrafluoroborate,
anhydride propanephosphonique,
imide de l'acide N-hydroxy-5-norbornène-2,3-dicarboxylique,
et N-hydroxy-1,2-dihydro-2-oxo-pyridine,
20 en présence éventuelle de base,
- pour conduire respectivement au composé de formule (Va) ou (Vb), selon que l'on est parti du composé de formule (IIIa) ou (IIIb) :



(Va)



(Vb)

dans laquelle R' est tel que défini précédemment,

que l'on soumet à une réaction d'hydrogénation catalytique en présence de palladium, pour conduire au produit de formule (I).

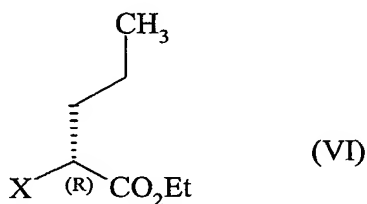
Parmi les groupements protecteurs de la fonction amino utilisables dans la présente invention, on peut citer à titre non limitatif les groupements tert-butyloxycarbonyl, benzyle et benzyloxycarbonyl.

L'hydrogénation catalytique du composé de formule (Va) est préférentiellement effectuée sous une pression d'hydrogène inférieure à 10 bars.

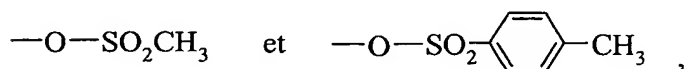
L'hydrogénation catalytique du composé de formule (Vb) est préférentiellement effectuée sous une pression d'hydrogène comprise entre 10 et 35 bars.

10 Le composé de formule (I) ainsi obtenu est ensuite soumis, le cas échéant, à une réaction de déprotection de la fonction amino, suivie d'une réaction de couplage, soit avec le 2-oxo-pentanoate d'éthyle dans des conditions d'amination réductrice,

soit avec un composé de formule (VI) :



15 dans laquelle X représente un groupement partant choisi parmi atome d'halogène,



pour conduire au perindopril optiquement pur, que l'on transforme, si on le souhaite, en un sel pharmaceutiquement acceptable tel que le sel de tert-butylamine.

Les exemples ci-dessous illustrent l'invention.

Exemple 1 : *Acide (2S, 3aS, 7aS)-1-[(2S)-2-[(tert-butyloxycarbonyl)-amino]-propionyl]-octahydro-1H-indole-2-carboxylique / méthode 1 :*

Stade A : *(2S, 3aS, 7aS)-1-[(2S)-2-[(Tert-butyloxycarbonyl)-amino]-propionyl]-octahydro-1H-indole-2-carboxylate de benzyle :*

- 5 Dans un réacteur sous agitation sont introduits 200 g du paratoluènesulfonate de l'ester benzylique de l'acide (2S, 3aS, 7aS)-octahydroindole 2-carboxylique, 65 ml de triéthylamine, 1 l d'acétate d'éthyle puis, après 10 mn d'agitation à température ambiante, 87 g de N-[tert-butyloxycarbonyl]-(S)-alanine, et 175 g de O-(benzotriazol-1-yl)-1,1,3,3-bis(tétraméthylène)-uronium hexafluorophosphate. Le mélange hétérogène est ensuite
10 porté à 30°C pendant 3h sous bonne agitation, puis il est refroidi à 0°C et filtré.
Le filtrat est ensuite lavé, puis évaporé à sec pour conduire au produit attendu.

Stade B : *Acide (2S, 3aS, 7aS)-1-[(2S)-2-[(tert-butyloxycarbonyl)-amino]-propionyl]-octahydro-1H-indole-2-carboxylique :*

- Le résidu obtenu dans le stade précédent (200 g) est mis en solution dans 200 ml de
15 méthylcyclohexane et transféré dans un hydrogénateur, puis 26 g de charbon palladié à 5% en suspension dans 80 ml de méthylcyclohexane sont ajoutés, suivis de 640 ml d'eau.
Le mélange est ensuite hydrogéné sous une pression de 0,5 bar, à une température comprise entre 15 et 30°C, jusqu'à absorption de la quantité théorique d'hydrogène.
Après filtration du catalyseur, la phase aqueuse du filtrat est lavée par du
20 méthylcyclohexane, puis lyophilisée pour conduire au produit attendu avec un rendement de 94%.

Exemple 2 : *Acide (2S, 3aS, 7aS)-1-[(2S)-2-[(tert-butyloxycarbonyl)-amino]-propionyl]-octahydro-1H-indole-2-carboxylique / méthode 2 :*

- Stade A :** *(2S)-1-[(2S)-2-[(Tert-butyloxycarbonyl)-amino]-propionyl]-2,3-dihydro-1H-indole-2-carboxylate de benzyle :*
- 25

Dans un réacteur sous agitation sont introduits 200 g du paratoluènesulfonate du 2,3-dihydro-1*H*-indole-2-carboxylate de benzyle, 66 ml de triéthylamine, 1 l d'acétate d'éthyle puis, après 10 mn d'agitation à température ambiante, 89 g de N-[tert-butyloxycarbonyl]-(*S*)-alanine, et 151 g de O-(benzotriazol-1-yl)-1,1,3,3-bis(tétraméthylène)-uronium
5 tétrafluoroborate. Le mélange hétérogène est ensuite porté à 30°C pendant 3h sous bonne agitation, puis il est refroidi à 0°C et filtré.

Le filtrat est ensuite lavé, puis évaporé à sec pour conduire au produit attendu.

Stade B : *Acide (2*S*, 3*aS*, 7*aS*)-1-{(2*S*)-2-[(tert-butyloxycarbonyl)-amino]-propionyl}-octahydro-1*H*-indole-2-carboxylique* :

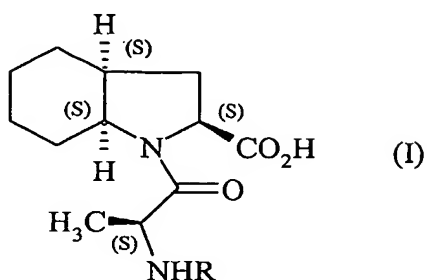
10 Le résidu obtenu dans le stade précédent (200 g) est mis en solution dans 200 ml de méthylcyclohexane et transféré dans un hydrogénateur, puis 26 g de charbon palladié à 5% en suspension dans 80 ml de méthylcyclohexane sont ajoutés, suivis de 640 ml d'eau.

Le mélange est ensuite hydrogéné sous une pression de 0,5 bar, à une température comprise entre 15 et 30°C, jusqu'à absorption de la quantité théorique d'hydrogène
15 nécessaire à la débenzylation, puis le mélange est porté à une température comprise entre 50 et 100°C et hydrogéné sous une pression de 30 bars, jusqu'à absorption de la quantité théorique d'hydrogène nécessaire à l'hydrogénation du cycle.

Après filtration du catalyseur, la phase aqueuse du filtrat est lavée par du méthylcyclohexane, puis lyophilisée pour conduire au produit attendu.

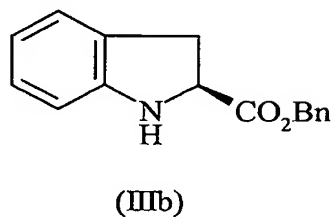
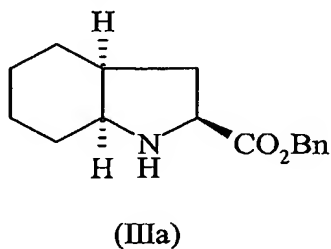
REVENDICATIONS

1. Procédé de synthèse des composés de formule (I)



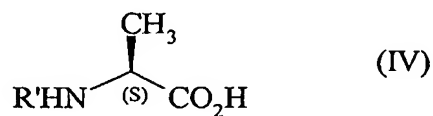
dans laquelle R représente un atome d'hydrogène ou un groupement protecteur de la
5 fonction amino,

caractérisé en ce que l'on met en réaction l'ester benzylique de formule (IIIa) ou (IIIb) :



ou le sel d'addition de l'ester de formule (IIIa) ou (IIIb) avec un acide minéral ou
organique,

10 avec le dérivé de l'alanine de formule (IV) :



dans laquelle R' représente un groupement protecteur de la fonction amino,

en présence d'un agent de couplage choisi parmi les réactifs et couples de réactifs suivants :

(1,3-diméthylaminopropyl)-3-éthyl-carbodiimide chlorhydrate,

15 (1,3-diméthylaminopropyl)-3-éthyl-carbodiimide chlorhydrate / 1-hydroxybenzotriazole,

- (1,3-diméthylaminopropyl)-3-éthyl-carbodiimide chlorhydrate/1-hydroxy-7-azabenzotriazole,
(1,3-diméthylaminopropyl)-3-éthyl-carbodiimide chlorhydrate / N-hydroxysuccinimide,
(1,3-diméthylaminopropyl)-3-éthyl-carbodiimide chlorhydrate /3-hydroxy-3,4-dihydro-4-
5 oxo-1,2,3-benzotriazine,
(1,3-diméthylaminopropyl)-3-éthyl-carbodiimide chlorhydrate / N-hydroxyphtalimide,
dicyclohexylcarbodiimide / 1-hydroxy-7-azabenzotriazole,
dicyclohexylcarbodiimide / N-hydroxysuccinimide,
dicyclohexylcarbodiimide /3-hydroxy-3,4-dihydro-4-oxo-1,2,3-benzotriazine,
10 dicyclohexylcarbodiimide / N-hydroxyphtalimide,
O-(benzotriazol-1-yl)-1,1,3,3-tétraméthyluronium hexafluorophosphate,
O-(7-azabenzotriazol-1-yl)-1,1,3,3-tétraméthyluronium hexafluorophosphate,
O-(benzotriazol-1-yl)-1,1,3,3-tétraméthyluronium tétrafluoroborate,
benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate,
15 benzotriazol-1-yl-oxy-tris-(diméthylamino)-phosphonium hexafluorophosphate,
O-(benzotriazol-1-yl)-1,1,3,3-bis(tétraméthylène)-uronium hexafluorophosphate,
O-(benzotriazol-1-yl)-1,1,3,3-bis(pentaméthylène)-uronium hexafluorophosphate,
chloro-tripyrrolidinophosphonium hexafluorophosphate,
chloro-1,1,3,3-bis(tétraméthylène)-formamidinium hexafluorophosphate,
20 chloro-1,1,3,3-bis(pentaméthylène)-formamidinium hexafluorophosphate,
N-éthoxycarbonyl-2-éthoxy-1,2-dihydroquinoléine,
O-[(éthoxycarbonyl)-cyanométhylénamino]-1,1,3,3- tétraméthyluronium tétrafluoroborate,
O-(3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl)-1,1,3,3-tétraméthyluronium
tétrafluoroborate,
25 O-(3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl)-1,1,3,3-tétraméthyluronium
tétrafluoroborate /1-hydroxybenzotriazole,
O-(3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl)-1,1,3,3-tétraméthyluronium
tétrafluoroborate /N-méthylmorpholine,
O-(3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl)-1,1,3,3-tétraméthyluronium
30 tétrafluoroborate /collidine,
O-(1,2-dihydro-2-oxo-1-pyridyl)-1,1,3,3-tétraméthyluronium tétrafluoroborate,

O-(1,2-dihydro-2-oxo-1-pyridyl)-1,1,3,3-tétraméthyluronium tétrafluoroborate/1-hydroxy-benzotriazole,

O-(1,2-dihydro-2-oxo-1-pyridyl)-1,1,3,3-bis(tétraméthylène)-uronium hexafluorophosphate,

5 O-(1,2-dihydro-2-oxo-1-pyridyl)-1,1,3,3-bis(tétraméthylène)-uronium hexafluorophosphate/1-hydroxy-benzotriazole,

O-(N-succinimidyl)-1,1,3,3-tétraméthyluronium tétrafluoroborate,

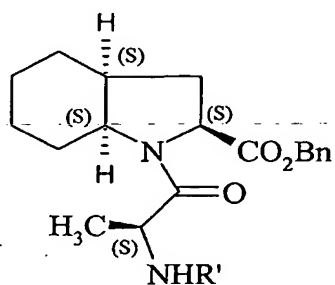
O-(N-succinimidyl)-1,1,3,3-bis(tétraméthylène)uronium tétrafluoroborate,

10 O-(N-succinimidyl)-1,1,3,3-bis(tétraméthylène)uronium tétrafluoroborate/1-hydroxy-benzotriazole,

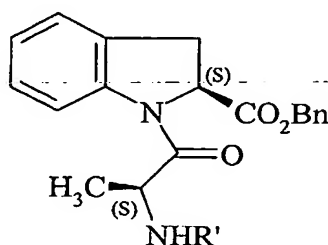
O-(5-norbornène-2,3-dicarboximido)-1,1,3,3-tétraméthyluronium tétrafluoroborate, anhydride propanephosphonique,

imide de l'acide N-hydroxy-5-norbornène-2,3-dicarboxylique, et N-hydroxy-1,2-dihydro-2-oxo-pyridine,

15 en présence éventuelle de base, pour conduire respectivement au composé de formule (Va) ou (Vb), selon que l'on est parti du composé de formule (IIIa) ou (IIIb) :



(Va)



(Vb)

dans laquelle R' est tel que défini précédemment,

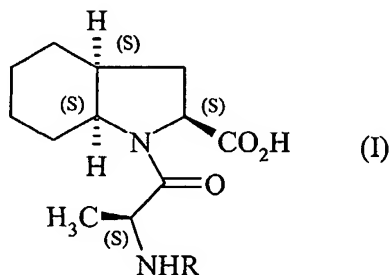
20 que l'on soumet à une réaction d'hydrogénation catalytique en présence de palladium, pour conduire au produit de formule (I).

2. Procédé selon la revendication 1, caractérisé en ce que l'on part du composé de formule (IIIa).
3. Procédé selon la revendication 1, caractérisé en ce que l'on part du composé de formule (IIIb).
- 5 4. Procédé selon la revendication 2, caractérisé en ce que la réaction d'hydrogénation du composé de formule (Va) est effectuée sous une pression d'hydrogène inférieure à 10 bars.
5. Procédé selon la revendication 3, caractérisé en ce que la réaction d'hydrogénation du composé de formule (Vb) est effectuée sous une pression d'hydrogène comprise entre
10 10 et 35 bars.
6. Procédé de synthèse du perindopril ou de ses sels pharmaceutiquement acceptables à partir du composé de formule (I), caractérisé en ce que le composé de formule (I) est obtenu par le procédé de synthèse selon l'une quelconque des revendications 1 à 5.

ABREGE

**NOUVEAU PROCEDE DE SYNTHESE DE DERIVES DE L'ACIDE (2S, 3aS, 7aS)-
1-[(S)-ALANYL]-OCTAHYDRO-1H-INDOLE-2-CARBOXYLIQUE ET
APPLICATION A LA SYNTHESE DU PERINDOPRIL**

5 Procédé de synthèse des composés de formule (I) :



10 dans laquelle R. représente un atome d'hydrogène ou un groupement protecteur de la
fonction amino.

Application à la synthèse du perindopril et de ses sels pharmaceutiquement acceptables.

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European
Patent Office

Certificate

The attached documents
are exact copies of the
European patent application
described on the following
page, as originally filed.

Patent application No.

03293085.1

For the President of the
European Patent Office

[signature]

R C van Dijk

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European
Patent Office

Application no.: 03293085.1

Date of filing: 10.12.03

Applicant(s):

Les Laboratoires Servier
12, Place de La Défense
92415 Courbevoie Cedex
FRANCE

Title of the invention:

(If no title is shown please refer to the description.)

New process for the synthesis of (2S,3aS,7aS)-1-[(S)-alanyl]-octahydro-1H-indole-2-carboxylic acid compounds and application in the synthesis of perindopril

Priority(ies) claimed

State/Date/File no.:

International Patent classification:

C07D209/00

Contracting states designated at date of filing:

AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL
PT RO SE SI SK TR LI

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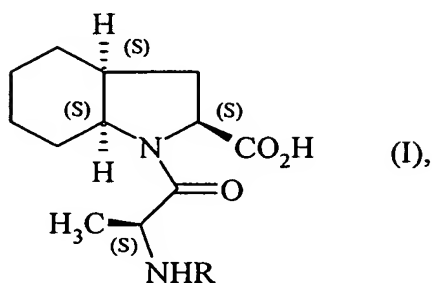
**NEW PROCESS FOR THE SYNTHESIS OF (2S,3aS,7aS)-1-[(S)-ALANYL]-
OCTAHYDRO-1*H*-INDOLE-2-CARBOXYLIC ACID COMPOUNDS AND
APPLICATION IN THE SYNTHESIS OF PERINDOPRIL**

**LES LABORATOIRES SERVIER
12, PLACE DE LA DEFENSE
F-92415 COURBEVOIE CEDEX**

**INVENTORS : T. DUBUFFET
 J-P LECOUE**

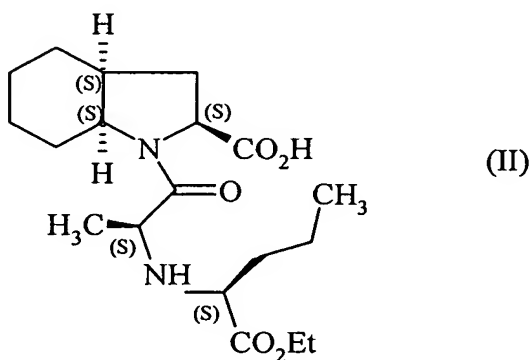
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The present invention relates to a process for the synthesis of compounds of formula (I) :



wherein R represents a hydrogen atom or a protecting group for the amino function,

and to their application in the synthesis of perindopril of formula (II) :



5

and pharmaceutically acceptable salts thereof.

Perindopril and its pharmaceutically acceptable salts, and more especially its tert-butylamine salt, have valuable pharmacological properties.

Their principal property is that of inhibiting angiotensin I converting enzyme (or
 10 kininase II), which allows, on the one hand, prevention of the conversion of the decapeptide angiotensin I to the octapeptide angiotensin II (a vasoconstrictor) and, on the other hand, prevention of the degradation of bradykinin (a vasodilator) to an inactive peptide.

Those two actions contribute to the beneficial effects of perindopril in cardiovascular
 15 diseases, more especially in arterial hypertension and heart failure.

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Perindopril, its preparation and its use in therapeutics have been described in European patent specification EP 0 049 658.

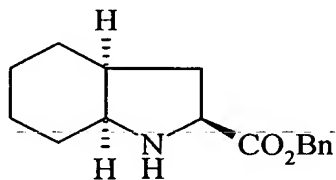
In view of the pharmaceutical value of this compound, it has been important to be able to obtain it by an effective synthesis process, readily transposable to an industrial scale, that leads to perindopril in a good yield and with excellent purity.

Patent specification EP 0 308 341 describes the industrial synthesis of perindopril by the coupling of (2*S*,3*aS*,7*aS*)-octahydroindole-2-carboxylic acid benzyl ester with N-[(*S*)-1-carboxybutyl]-(*S*)-alanine ethyl ester in the presence of dicyclohexylcarbodiimide, followed by deprotection of the carboxylic group of the heterocycle by catalytic hydrogenation.

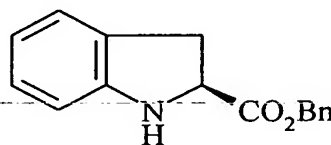
That process has disadvantages related to use of the dicyclohexylcarbodiimide.

The Applicant has developed a process for the synthesis of perindopril that uses other coupling agents.

More specifically, the present invention relates to a process for the synthesis of perindopril, which process is characterised in that the benzyl ester of formula (IIIa) or (IIIb) :



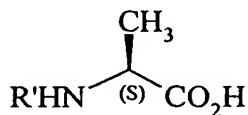
(IIIa)



(IIIb)

or an addition salt of the ester of formula (IIIa) or (IIIb) with a mineral acid or organic acid is reacted

with the alanine compound of formula (IV) :



(IV),

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wherein R' represents a protecting group for the amino function,

in the presence of a coupling agent selected from the following reagents and pairs of reagents :

- (1,3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride,
- 5 (1,3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride / 1-hydroxybenzotriazole,
- (1,3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride / 1-hydroxy-7-azabenzotriazole,
- (1,3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride / N-hydroxysuccinimide,
- (1,3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride / 3-hydroxy-3,4-dihydro-
- 10 4-oxo-1,2,3-benzotriazine,
- (1,3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride / N-hydroxyphthalimide,
- dicyclohexylcarbodiimide / 1-hydroxy-7-azabenzotriazole,
- dicyclohexylcarbodiimide / N-hydroxysuccinimide,
- dicyclohexylcarbodiimide / 3-hydroxy-3,4-dihydro-4-oxo-1,2,3-benzotriazine,
- 15 dicyclohexylcarbodiimide / N-hydroxyphthalimide,
- O-(benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate,
- O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate,
- O-(benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate,
- benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate,
- 20 benzotriazol-1-yl-oxy-tris(dimethylamino)phosphonium hexafluorophosphate,
- O-(benzotriazol-1-yl)-1,1,3,3-bis(tetramethylene)uronium hexafluorophosphate,
- O-(benzotriazol-1-yl)-1,1,3,3-bis(pentamethylene)uronium hexafluorophosphate,
- chloro-tripyrrolidinophosphonium hexafluorophosphate,
- chloro-1,1,3,3-bis(tetramethylene)formamidinium hexafluorophosphate,
- 25 chloro-1,1,3,3-bis(pentamethylene)formamidinium hexafluorophosphate,
- N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline,
- O-[(ethoxycarbonyl)-cyanomethyleneamino]-1,1,3,3-tetramethyluronium tetrafluoroborate,
- O-(3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl)-1,1,3,3-tetramethyluronium tetrafluoro-
- borate,
- 30 O-(3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl)-1,1,3,3-tetramethyluronium tetrafluoro-
- borate / 1-hydroxybenzotriazole,

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O-(3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate / N-methylmorpholine,

O-(3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate / collidine,

5 O-(1,2-dihydro-2-oxo-1-pyridyl)-1,1,3,3-tetramethyluronium tetrafluoroborate,

O-(1,2-dihydro-2-oxo-1-pyridyl)-1,1,3,3-tetramethyluronium tetrafluoroborate / 1-hydroxybenzotriazole,

O-(1,2-dihydro-2-oxo-1-pyridyl)-1,1,3,3-bis(tetramethylene)uronium hexafluorophosphate,

O-(1,2-dihydro-2-oxo-1-pyridyl)-1,1,3,3-bis(tetramethylene)uronium hexafluoro-

10 phosphate / 1-hydroxy-benzotriazole,

O-(N-succinimidyl)-1,1,3,3-tetramethyluronium tetrafluoroborate,

O-(N-succinimidyl)-1,1,3,3-bis(tetramethylene)uronium tetrafluoroborate,

O-(N-succinimidyl)-1,1,3,3-bis(tetramethylene)uronium tetrafluoroborate / 1-hydroxy-benzotriazole,

15 O-(5-norbornene-2,3-dicarboximido)-1,1,3,3-tetramethyluronium tetrafluoroborate,

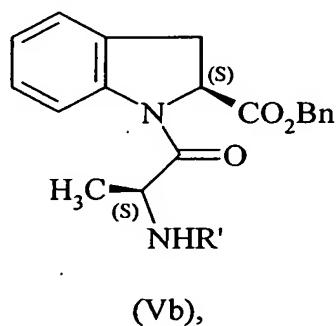
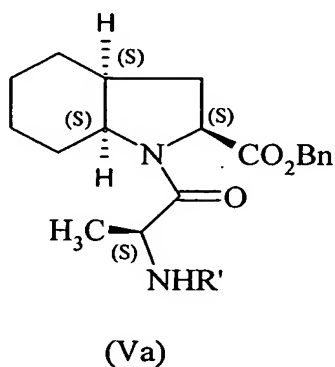
propanephosphonic anhydride,

N-hydroxy-5-norbornene-2,3-dicarboxylic acid imide,

and N-hydroxy-1,2-dihydro-2-oxo-pyridine,

optionally in the presence of a base,

20 to yield the compound of formula (Va) or (Vb), respectively, depending on whether the compound of formula (IIIa) or (IIIb) is used as starting material :



wherein R' is as defined hereinbefore,

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which is subjected to a catalytic hydrogenation reaction in the presence of palladium to yield the product of formula (I).

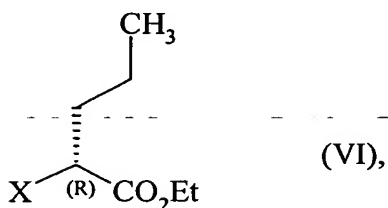
Among the protecting groups for the amino function which can be used in the present invention, there may be mentioned, without implying any limitation, the tert-
5 butyloxycarbonyl, benzyl and benzyloxycarbonyl groups.

The catalytic hydrogenation of the compound of formula (Va) is preferably carried out under a hydrogen pressure of less than 10 bars.

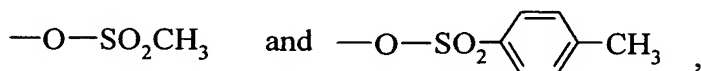
The catalytic hydrogenation of the compound of formula (Vb) is preferably carried out under a hydrogen pressure of from 10 to 35 bars.

10 The compound of formula (I) thereby obtained is then subjected, if required, to a reaction deprotecting the amino function, followed by a coupling reaction either with ethyl 2-oxo-pentanoate under conditions of reductive amination

or with a compound of formula (VI) :



15 wherein X represents a leaving group selected from halogen,



to yield optically pure perindopril, which is converted, if desired, into a pharmaceutically acceptable salt such as the tert-butylamine salt.

The Examples hereinbelow illustrate the invention.

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Example 1 : *(2S,3aS,7aS)-1-[(2S)-2-[(tert-Butyloxycarbonyl)-amino]-propionyl]-octahydro-1H-indole-2-carboxylic acid / method 1 :*

Step A : *Benzyl (2S,3aS,7aS)-1-[(2S)-2-[(tert-butyloxycarbonyl)-amino]-propionyl]-octahydro-1H-indole-2-carboxylate :*

- 5 200 g of (2S,3aS,7aS)-octahydroindole-2-carboxylic acid benzyl ester para-toluene-sulphonate, 65 ml of triethylamine and 1 litre of ethyl acetate are introduced into a stirred reactor, followed, after stirring for 10 minutes at ambient temperature, by 87 g of N-[tert-butyloxycarbonyl]-(S)-alanine and 175 g of O-(benzotriazol-1-yl)-1,1,3,3-bis(tetramethylene)uronium hexafluorophosphate. The heterogeneous mixture is then heated at
- 10 30°C for 3 hours whilst stirring well and is then cooled to 0°C and filtered.
- The filtrate is then washed and subsequently evaporated to dryness to yield the expected product.

Step B : *(2S,3aS,7aS)-1-[(2S)-2-[(tert-Butyloxycarbonyl)-amino]-propionyl]-octahydro-1H-indole-2-carboxylic acid :*

- 15 The residue obtained in the previous Step (200 g) is dissolved in 200 ml of methylcyclohexane and transferred to a hydrogenator; 26 g of 5 % palladium-on-carbon suspended in 80 ml of methylcyclohexane are then added, followed by 640 ml of water.
- The mixture is then hydrogenated under a pressure of 0.5 bar at a temperature of from 15 to 30°C, until the theoretical amount of hydrogen has been absorbed.
- 20 After filtering off the catalyst, the aqueous phase of the filtrate is washed with methylcyclohexane and then lyophilised to yield the expected product in a yield of 94 %.

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Example 2 : *(2S,3aS,7aS)-1-{(2S)-2-[(tert-Butyloxycarbonyl)-amino]-propionyl}-octahydro-1H-indole-2-carboxylic acid / method 2 :*

Step A : *Benzyl (2S)-1-{(2S)-2-[(tert-butyloxycarbonyl)-amino]-propionyl}-2,3-dihydro-1H-indole-2-carboxylate :*

- 5 200 g of benzyl 2,3-dihydro-1H-indole-2-carboxylate para-toluenesulphonate, 66 ml of triethylamine and 1 litre of ethyl acetate are introduced into a stirred reactor, followed, after stirring for 10 minutes at ambient temperature, by 89 g of N-[tert-butyloxycarbonyl]-(S)-alanine and 151 g of O-(benzotriazol-1-yl)-1,1,3,3-bis(tetramethylene)uronium tetrafluoroborate. The heterogeneous mixture is then heated at 30°C for 3 hours whilst
- 10 stirring well and is then cooled to 0°C and filtered.
- The filtrate is then washed and subsequently evaporated to dryness to yield the expected product.

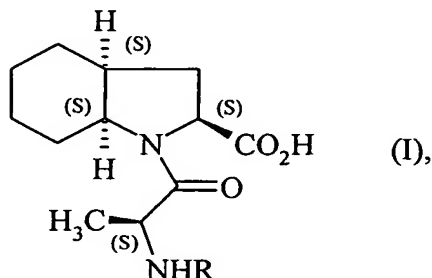
Step B : *(2S,3aS,7aS)-1-{(2S)-2-[(tert-Butyloxycarbonyl)-amino]-propionyl}-octahydro-1H-indole-2-carboxylic acid :*

- 15 The residue obtained in the previous Step (200 g) is dissolved in 200 ml of methylcyclohexane and transferred to a hydrogenator; 26 g of 5 % palladium-on-carbon suspended in 80 ml of methylcyclohexane are then added, followed by 640 ml of water.
- 20 The mixture is then hydrogenated under a pressure of 0.5 bar at a temperature of from 15 to 30°C, until the theoretical amount of hydrogen required for debenzylation has been absorbed; the mixture is then heated to a temperature of from 50 to 100°C and hydrogenated under a pressure of 30 bars until the theoretical amount of hydrogen required for hydrogenation of the ring has been absorbed.
- After filtering off the catalyst, the aqueous phase of the filtrate is washed with methylcyclohexane and then lyophilised to yield the expected product.

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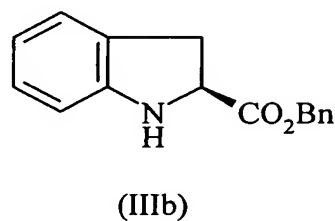
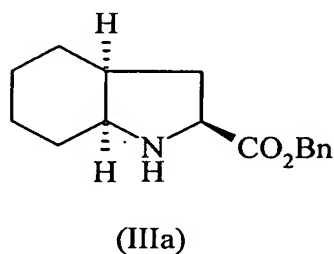
CLAIMS

1. Process for the synthesis of compounds of formula (I)



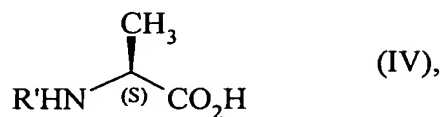
wherein R represents a hydrogen atom or a protecting group for the amino function,

5 characterised in that the benzyl ester of formula (IIIa) or (IIIb) :



or an addition salt of the ester of formula (IIIa) or (IIIb) with a mineral acid or organic acid is reacted

with the alanine compound of formula (IV) :



wherein R' represents a protecting group for the amino function,

in the presence of a coupling agent selected from the following reagents and pairs of reagents :

(1,3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride,

15 (1,3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride / 1-hydroxybenzotriazole,

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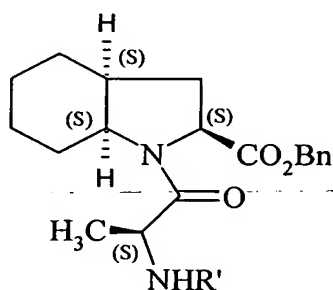
- (1,3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride / 1-hydroxy-7-azabenzotriazole,
(1,3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride / N-hydroxysuccinimide,
(1,3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride / 3-hydroxy-3,4-dihydro-
5 4-oxo-1,2,3-benzotriazine,
(1,3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride / N-hydroxyphthalimide,
dicyclohexylcarbodiimide / 1-hydroxy-7-azabenzotriazole,
dicyclohexylcarbodiimide / N-hydroxysuccinimide,
dicyclohexylcarbodiimide / 3-hydroxy-3,4-dihydro-4-oxo-1,2,3-benzotriazine,
10 dicyclohexylcarbodiimide / N-hydroxyphthalimide,
O-(benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate,
O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate,
O-(benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate,
benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate,
15 benzotriazol-1-yl-oxy-tris(dimethylamino)phosphonium hexafluorophosphate,
O-(benzotriazol-1-yl)-1,1,3,3-bis(tetramethylene)uronium hexafluorophosphate,
O-(benzotriazol-1-yl)-1,1,3,3-bis(pentamethylene)uronium hexafluorophosphate,
chloro-tripyrrolidinophosphonium hexafluorophosphate,
chloro-1,1,3,3-bis(tetramethylene)formamidinium hexafluorophosphate,
20 chloro-1,1,3,3-bis(pentamethylene)formamidinium hexafluorophosphate,
N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline,
O-[(ethoxycarbonyl)-cyanomethyleneamino]-1,1,3,3-tetramethyluronium tetrafluoroborate,
O-(3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl)-1,1,3,3-tetramethyluronium tetrafluoro-
borate,
25 O-(3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl)-1,1,3,3-tetramethyluronium tetrafluoro-
borate / 1-hydroxybenzotriazole,
O-(3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl)-1,1,3,3-tetramethyluronium tetrafluoro-
borate / N-methylmorpholine,
O-(3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl)-1,1,3,3-tetramethyluronium tetrafluoro-
30 borate / collidine,
O-(1,2-dihydro-2-oxo-1-pyridyl)-1,1,3,3-tetramethyluronium tetrafluoroborate,

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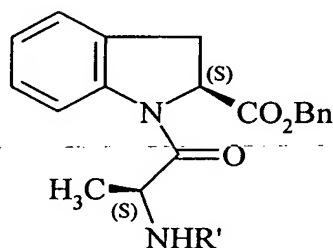
O-(1,2-dihydro-2-oxo-1-pyridyl)-1,1,3,3-tetramethyluronium tetrafluoroborate /
 1-hydroxybenzotriazole,
 O-(1,2-dihydro-2-oxo-1-pyridyl)-1,1,3,3-bis(tetramethylene)uronium hexafluorophosphate,
 O-(1,2-dihydro-2-oxo-1-pyridyl)-1,1,3,3-bis(tetramethylene)uronium hexafluoro-
 5 phosphate / 1-hydroxy-benzotriazole,
 O-(N-succinimidyl)-1,1,3,3-tetramethyluronium tetrafluoroborate,
 O-(N-succinimidyl)-1,1,3,3-bis(tetramethylene)uronium tetrafluoroborate,
 O-(N-succinimidyl)-1,1,3,3-bis(tetramethylene)uronium tetrafluoroborate / 1-hydroxy-
 benzotriazole,
 10 O-(5-norbornene-2,3-dicarboximido)-1,1,3,3-tetramethyluronium tetrafluoroborate,
 propanephosphonic anhydride,
 N-hydroxy-5-norbornene-2,3-dicarboxylic acid imide,
 and N-hydroxy-1,2-dihydro-2-oxo-pyridine,

optionally in the presence of a base,

15 to yield the compound of formula (Va) or (Vb), respectively, depending on whether the
 compound of formula (IIIa) or (IIIb) is used as starting material :



(Va)



(Vb),

wherein R' is as defined hereinbefore,

20 which is subjected to a catalytic hydrogenation reaction in the presence of palladium to
 yield the product of formula (I).

2. Process according to claim 1, characterised in that the compound of formula (IIIa) is
 used as starting material.

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3. Process according to claim 1, characterised in that the compound of formula (IIIb) is used as starting material.

4. Process according to claim 2, characterised in that the hydrogenation reaction on the compound of formula (Va) is carried out under a hydrogen pressure of less than 10 bars.

5. Process according to claim 3, characterised in that the hydrogenation reaction on the compound of formula (Vb) is carried out under a hydrogen pressure of from 10 to 35 bars.

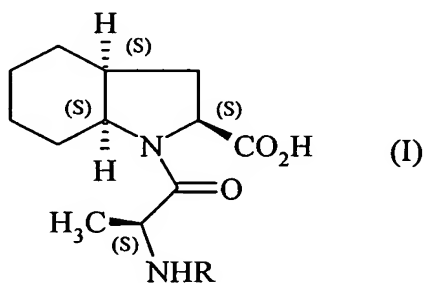
6. Process for the synthesis of perindopril or pharmaceutically acceptable salts thereof starting from a compound of formula (I), characterised in that the said compound of formula (I) is obtained by the synthesis process according to any one of claims 1 to 5.

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ABSTRACT

**NEW PROCESS FOR THE SYNTHESIS OF (2S,3aS,7aS)-1-[(S)-ALANYL]-
OCTAHYDRO-1H-INDOLE-2-CARBOXYLIC ACID COMPOUNDS AND
APPLICATION IN THE SYNTHESIS OF PERINDOPRIL**

- 5 Process for the synthesis of compounds of formula (I) :



wherein R represents a hydrogen atom or a protecting group for the amino function.

- 10 Application in the synthesis of perindopril and pharmaceutically acceptable salts thereof.

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PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference
(if desired) (12 characters maximum) 9490-P29

Box No. I TITLE OF INVENTION

New process for the synthesis of (2S,3aS,7aS)-1-[(S)-alanyl]-octahydro-1H-indole-2-carboxylic acid compounds and application in the synthesis of perindopril

Box No. II APPLICANT

☐ This person is also inventor

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

LES LABORATOIRES SERVIER
12, Place de la Défense
92415 COURBEVOIE Cedex
FRANCE

Telephone No.
01.55.72.60.00

Facsimile No.
01.55.72.72.13

Teleprinter No.

Applicant's registration No. with the Office

State (that is, country) of nationality:

FR

State (that is, country) of residence:

FR

This person is applicant
for the purposes of:

☐ all designated
States

☒ all designated States except
the United States of America

☐ the United States
of America only

☐ the States indicated in
the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

DUBUFFET, Thierry
17, allée des Charmilles
76190 AUTRETOT
FRANCE

This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only (If this check-box is
marked, do not fill in below.)

Applicant's registration No. with the Office

State (that is, country) of nationality:

FR

State (that is, country) of residence:

FR

This person is applicant
for the purposes of:

☐ all designated
States

☐ all designated States except
the United States of America

☒ the United States
of America only

☐ the States indicated in
the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf
of the applicant(s) before the competent International Authorities as:

☐ agent

☒ common
representative

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

LES LABORATOIRES SERVIER
12, Place de la défense
92415 COURBEVOIE Cedex
FRANCE

Telephone No.
01.55.72.60.00

Facsimile No.
01.55.72.72.13

Teleprinter No.

Agent's registration No. with the Office

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

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Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)*If none of the following sub-boxes is used, this sheet should not be included in the request.*

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

LECOUVE, Jean-Pierre
93, rue du Docteur Vigné
76600 LE HAVRE
FRANCE

This person is:

- ☐ applicant only
☒ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

Applicant's registration No. with the Office

State (that is, country) of nationality:
FR

State (that is, country) of residence:
FR

This person is applicant for the purposes of:

- ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

This person is:

- ☐ applicant only
☐ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

Applicant's registration No. with the Office

State (that is, country) of nationality:

State (that is, country) of residence:

This person is applicant for the purposes of:

- ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

This person is:

- ☐ applicant only
☐ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

Applicant's registration No. with the Office

State (that is, country) of nationality:

State (that is, country) of residence:

This person is applicant for the purposes of:

- ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

This person is:

- ☐ applicant only
☐ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

Applicant's registration No. with the Office

State (that is, country) of nationality:

State (that is, country) of residence:

This person is applicant for the purposes of:

- ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

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Box No. V DESIGNATIONS

The filing of this request constitutes under Rule 4.9(a), the designation of all Contracting States bound by the PCT on the international filing date, for the grant of every kind of protection available and, where applicable, for the grant of both regional and national patents.

However,

- ☐ DE Germany is not designated for any kind of national protection
- ☐ KR Republic of Korea is not designated for any kind of national protection
- ☐ RU Russian Federation is not designated for any kind of national protection

(The check-boxes above may be used to exclude (irrevocably) the designations concerned in order to avoid the ceasing of the effect, under the national law, of an earlier national application from which priority is claimed. See the Notes to Box No. V as to the consequences of such national law provisions in these and certain other States.)

Box No. VI PRIORITY CLAIM

The priority of the following earlier application(s) is hereby claimed:

Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is:		
		national application: country or Member of WTO	regional application:* regional Office	international application: receiving Office
item (1) 10 December 2003 (10/12/03)	03293085.1		EP	
item (2)				
item (3)				

☐ Further priority claims are indicated in the Supplemental Box.

The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) (only if the earlier application was filed with the Office which for the purposes of this international application is the receiving Office) identified above as:

☐ all items ☐ item (1) ☐ item (2) ☐ item (3) ☐ other, see Supplemental Box

* Where the earlier application is an ARIPO application, indicate at least one country party to the Paris Convention for the Protection of Industrial Property or one Member of the World Trade Organization for which that earlier application was filed (Rule 4.10(b)(ii)):

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) (if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):

ISA /

Request to use results of earlier search; reference to that search (if an earlier search has been carried out by or requested from the International Searching Authority):

Date (day/month/year) Number Country (or regional Office)

Box No. VIII DECLARATIONS

The following declarations are contained in Boxes Nos. VIII (i) to (v) (mark the applicable check-boxes below and indicate in the right column the number of each type of declaration):

Number of
declarations

- | | | |
|---|--|---|
| <input type="checkbox"/> Box No. VIII (i) | Declaration as to the identity of the inventor | : |
| <input type="checkbox"/> Box No. VIII (ii) | Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent | : |
| <input type="checkbox"/> Box No. VIII (iii) | Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application | : |
| <input type="checkbox"/> Box No. VIII (iv) | Declaration of inventorship (only for the purposes of the designation of the United States of America) | : |
| <input type="checkbox"/> Box No. VIII (v) | Declaration as to non-prejudicial disclosures or exceptions to lack of novelty | : |

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Box No. IX CHECK LIST; LANGUAGE OF FILING		
<p>This international application contains:</p> <p>(a) on paper, the following number of sheets:</p> <p style="margin-left: 20px;">request (including declaration sheets) : 4</p> <p style="margin-left: 20px;">description (excluding sequence listing and/or tables related thereto) : 7</p> <p style="margin-left: 20px;">claims : 4</p> <p style="margin-left: 20px;">abstract : 1</p> <p style="margin-left: 20px;">drawings : 16</p> <p style="margin-left: 20px;">Sub-total number of sheets : 16</p> <p style="margin-left: 20px;">sequence listing : 16</p> <p style="margin-left: 20px;">tables related thereto : 16</p> <p style="margin-left: 20px;">(for both, actual number of sheets if filed on paper, whether or not also filed in electronic form; see (c) below)</p> <p style="margin-left: 20px;">Total number of sheets : 16</p> <p>(b) <input type="checkbox"/> only in electronic form (Section 801(a)(i))</p> <p style="margin-left: 20px;">(i) <input type="checkbox"/> sequence listing</p> <p style="margin-left: 20px;">(ii) <input type="checkbox"/> tables related thereto</p> <p>(c) <input type="checkbox"/> also in electronic form (Section 801(a)(ii))</p> <p style="margin-left: 20px;">(i) <input type="checkbox"/> sequence listing</p> <p style="margin-left: 20px;">(ii) <input type="checkbox"/> tables related thereto</p> <p>Type and number of carriers (diskette, CD-ROM, CD-R or other) on which are contained the</p> <p style="margin-left: 20px;"><input type="checkbox"/> sequence listing:</p> <p style="margin-left: 20px;"><input type="checkbox"/> tables related thereto:</p> <p style="margin-left: 20px;">(additional copies to be indicated under items 9(ii) and/or 10(ii), in right column)</p>	<p>This international application is accompanied by the following item(s) (mark the applicable check-boxes below and indicate in right column the number of each item):</p> <p>1. <input type="checkbox"/> fee calculation sheet :</p> <p>2. <input checked="" type="checkbox"/> original separate power of attorney : 1</p> <p>3. <input type="checkbox"/> original general power of attorney :</p> <p>4. <input type="checkbox"/> copy of general power of attorney; reference number, if any: :</p> <p>5. <input type="checkbox"/> statement explaining lack of signature :</p> <p>6. <input checked="" type="checkbox"/> priority document(s) identified in Box No. VI as item(s): : 1</p> <p>7. <input type="checkbox"/> translation of international application into (language): :</p> <p>8. <input type="checkbox"/> separate indications concerning deposited microorganism or other biological material :</p> <p>9. <input type="checkbox"/> sequence listing in electronic form (indicate type and number of carriers)</p> <p style="margin-left: 20px;">(i) <input type="checkbox"/> copy submitted for the purposes of international search under Rule 13ter only (and not as part of the international application) :</p> <p style="margin-left: 20px;">(ii) <input type="checkbox"/> (only where check-box (b)(i) or (c)(i) is marked in left column) additional copies including, where applicable, the copy for the purposes of international search under Rule 13ter :</p> <p style="margin-left: 20px;">(iii) <input type="checkbox"/> together with relevant statement as to the identity of the copy or copies with the sequence listing mentioned in left column :</p> <p>10. <input type="checkbox"/> tables in electronic form related to sequence listing (indicate type and number of carriers)</p> <p style="margin-left: 20px;">(i) <input type="checkbox"/> copy submitted for the purposes of international search under Section 802(b-quater) only (and not as part of the international application) :</p> <p style="margin-left: 20px;">(ii) <input type="checkbox"/> (only where check-box (b)(ii) or (c)(ii) is marked in left column) additional copies including, where applicable, the copy for the purposes of international search under Section 802(b-quater) :</p> <p style="margin-left: 20px;">(iii) <input type="checkbox"/> together with relevant statement as to the identity of the copy or copies with the tables mentioned in left column :</p> <p>11. <input type="checkbox"/> other (specify): :</p>	<p>Number of items</p>
<p>Figure of the drawings which should accompany the abstract:</p>	<p>Language of filing of the international application: French</p>	
<p>Box No. X SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE</p> <p><i>Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).</i></p>		
<p>(signature)</p> <p>Odile OSTERMANN, authorised signatory LES LABORATOIRES SERVIER</p>		

For receiving Office use only	
<p>1. Date of actual receipt of the purported international application:</p>	<p>2. Drawings:</p> <p><input type="checkbox"/> received:</p> <p><input type="checkbox"/> not received:</p>
<p>3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:</p>	
<p>4. Date of timely receipt of the required corrections under PCT Article 11(2):</p>	
<p>5. International Searching Authority (if two or more are competent): ISA /</p>	<p>6. <input type="checkbox"/> Transmittal of search copy delayed until search fee is paid</p>

For International Bureau use only
<p>Date of receipt of the record copy by the International Bureau:</p>

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